HUNTINGTON MEDICAL RESEARCH INSTITUTES
NEUROLOGICAL RESEARCH LABORATORY
734 Fairmount Avenue
Pasadena, California 91105

Contract No. NO1-NS-82388

QUARTERLY PROGRESS REPORT
July 1 - Sept 30, 1998

Report No. 3

"SAFE AND EFFECTIVE STIMULATION OF NEURAL TISSUE"

William F. Agnew, Ph.D.
Douglas B. McCreery, Ph.D.
Leo Bullara, B.A.
Ted G.H. Yuen, Ph.D.

SUMMARY

We continued our studies of the effect of 7 hours of continuous stimulation on the response evoked in the pyramidal tract by the intracortical microstimulation. Our first report on the results of these studies appeared in QPR #1. The pyramidal (corticospinal) tract is a direct, albeit rather sparse, projection from the sensorimotor cortex to the spinal cord. A recording microelectrode implanted chronically in the tract permits monitoring of the neuronal activity induced by an array of stimulating microelectrodes in the sensorimotor (cruciate cortex). We have developed a procedure for recording the action potentials from individual corticospinal axons via a single small recording electrode.

Our studies demonstrated variable degrees of stimulation-induced depression of neuronal excitability (SIDNE) when 5 closely-spaced microelectrodes are pulsed continuously, in the interleaved mode, for 7 hours, at a frequency of 25- 50 Hz and at 1.6 to 4 nC/phase. SIDNE was minimal when the threshold of the neuronal response was reasonably high (10-12 μA) before the start of the 7 hours of continuous stimulation, and when the post stimulus latency was greater than 2 ms. These responses are probably from corticospinal neurons that are excited directly by the intracortical microstimulation, and which probably are not too close to tip of the stimulating microelectrode. Response whose pre-stimulus thresholds are low (and which therefore are probably generated by corticospinal neurons that are close to the stimulating microelectrode) tended to exhibit more SIDNE, even when the amplitude or the frequency of the stimulus was low. Recovery of neuronal excitability is a slow process; one neuron required 28 days to recover to its pre-stimulus threshold. Corticospinal neurons whose longer post-stimulus latencies suggest that they are excited transsynaptically exhibited much greater SIDNE, even when their pre-stimulus thresholds were quite high (10 μA or greater)..

We also monitored the stability of chronically-implanted arrays of intracortical stimulating microelectrodes, using the threshold of the response evoked in the pyramidal tract as an index of the array's stability. These studies require that we identify

and monitor, over an interval of many days, the threshold of the action potential from individual corticospinal neurons. These studies indicate that "floating" arrays of intracortical microelectrodes that have been implanted for more than 80 days may continue to move within the cortex. This is consistent with histological findings of linear glial scars which indicate that the microelectrodes have been migrating slowly through the cortex. Our most recent data suggest that the arrays become more stable after 80-100 days *in vivo.*

METHODS

Fabrication of the microelectrode arrays

The shafts of the discrete iridium microelectrodes are made from iridium wire, 35 μm in diameter. One end of each shaft is etched electrolytically to a cone with an included angle of 10° and with a blunt tip approximately 12 μm in diameter. After the tips have been shaped to the proper configuration, a Teflon-insulated wire lead is micro-welded near the upper end of the shaft. The shaft is then insulated with 4 thin coats of Epoxylite electrode varnish, and each layer of insulation is baked using a schedule recommended by the manufacturer.

The insulation is removed from the tip of the shafts by dielectric destruction. The surface area of the exposed tip is determined by measurement of the double-layer capacitance while the tip is immersed in phosphate-buffered saline solution, using fast (100 Hz) cyclic voltammetry. The surface areas of these electrodes ranged from 450 to 2,200 μm^2.

The individual microelectrodes are then assembled into arrays of 7, which extend 1.2 to 1.5 mm from an epoxy matrix. The matrix is 2 mm in diameter. The microelectrodes are then "activated" (a layer of high-valence iridium oxide formed by anodic conversion) by potentiodynamic cycling between -0.8 and +0.7 volts with respect to a saturated calomel electrode, with the microelectrodes immersed in saturated sodium phosphate solution. The activation process is terminated when each microelectrode has a total charge capacity of 200 nC.

Surgical Procedure

Aseptic technique is used during the surgical implantation of the microelectrodes arrays. Young adult cats of either sex are anesthetized initially with Ketamine with transition to a mixture of 70% nitrous oxide, 30% oxygen and 1.5% Halothane. The surgical procedure is carried out with the animal's head in a stereotaxic apparatus. The scalp and temporalis muscle are reflected and, using a Hall bone drill, a craniectomy is made over the left frontal cortex extending into the frontal sinus. The frontal air sinus is partly filled with bone cement.

Prior to implanting the intracortical microelectrode array, a monopolar recording

electrode, and its accompanying reference electrode, are implanted in the cat's pyramidal (corticospinal) tract in order to record neuronal activity evoked by the stimulating microelectrodes. The recording electrode is fabricated from 0.25 mm Teflon-insulated stainless steel wire. The exposed area at the tip of the stainless steel electrode wire is approximately 0.1 mm^2. In preparation for implantation, the wire is mounted in a sleeve-type cannula device, which is mounted in a stereotaxic assembly. A small burr hole is cut in the calvarium over the cerebellum, and a small incision is made in the dura. A stimulating macroelectrode (approximately 0.5 mm in diameter) is placed against the dura over the pre- or postcruciate gyrus. This macroelectrode can support a large stimulus current (1 to 2 mA, 150 µsec/ph, at 20 Hz) which excites many corticospinal neurons and thus produces a large compound action potential that can be used to guide the recording electrode into the pyramidal tract. When the tip of the electrode is in the pyramidal tract, the inner introducer is retracted, and the recording and reference electrode are sealed to the skull with bone cement.

In preparation for implanting the microelectrode array into the sensorimotor cortex, the percutaneous connector is mounted to the skull with stainless steel screws and methacrylate bone cement. A small flap, slightly larger than the array's superstructure matrix, is made in the dura over the postcruciate cortex, and the array of microelectrodes is inserted into the cortex with the aid of an axial introducer mounted on the stereotaxic frame. During the implantation, a vacuum holds the arrays against the orifice of the introducer tool. In our cat model, we have found that it is best not to suture the dura over the array, but we do cover the array with a sheet of perforated artificial dura (silastic sheeting), which rapidly becomes overgrown with dura. The silastic sheet prevents the array from floating out of the cortex, but it may engender some problems related to the long-term positional stability of the array. In the most recent cat, a patch of fascia resected from the temporalis muscle was substituted for the silastic sheet. The cortex and silastic disk are covered with Gelfoam and the skull defect is sealed with cranioplasty.

Stimulation protocols

The test stimulation protocols were conducted at least 45 days after the implant surgery. During the stimulation, the cats were lightly anesthetized with Propofol. We have determined that the electrical excitability of the corticospinal neurons is not altered by light Propofol anesthesia, and the cats are much easier to manage when lightly anesthetized than when awake and wearing the tethered backpack.

In each array, 5 of the 7 microelectrodes were pulsed continuously for 7 hours. The microelectrodes were pulsed either simultaneously or sequentially (interleaved stimulation). The stimulus was charge-balanced, controlled current biphasic pulse pairs, 150 μs/phase (cathodic phase first). The activated iridium microelectrodes were biased at +400 mV with respect to the implanted Ag/AgCl reference electrode.

Within 30 minutes after the end of the stimulation regimen, the cats were deeply anesthetized with pentobarbital and perfused through the aorta with ½ strength Karnovsky's fixative (2.5% glutaraldehyde, 2% paraformaldehyde and 0.1M sodium cacodylate buffer). The array of microelectrodes was removed from the cerebral cortex, after resection of the overlying connective tissue. The block containing the array tracks was resected, embedded in paraffin, sectioned serially in the horizontal plane (perpendicular to the shafts of the stimulating microelectrodes) at a thickness of 8 μm, and stained with Cresol Violet (Nissl stain).

Recording from the pyramidal track

The neuronal activity evoked in the ipsilateral pyramidal (corticospinal) tract by each of the intracortical microelectrodes was recorded at intervals after implantation of the electrodes, and also before and after the sessions of continuous stimulation. Due to the sparseness of the corticospinal projection from the feline sensorimotor cortex, it was necessary to summate (average) the response to 2048 successive stimulus pulses, in order to obtain an acceptable signal-to-noise ratio. Even after such averaging, most of the intracortical microelectrodes did not evoke a response that was large enough to be uniquely identified in successive recording sessions. When a response was present, it had the characteristics of having been generated by one, or a most, by a very few corticospinal neurons. This apparently is due to the sparseness of

the corticospinal projection, and the fact that any corticospinal neurons that are excited must pass very close to the pyramidal tract recording electrodes, in order for their action potentials to be detected.

RESULTS

The effects of 7 hours of intracortical microstimulation on the excitability of corticospinal neurons.

Figure 1A shows one type of neuronal response that we recorded in the ipsilateral pyramidal tract, in response to microstimulation in the pre- or postcruciate gyrus of the cat cerebral cortex. Each trace was obtained by summating the response to 2,048 consecutive stimulus pulses, delivered at 20 Hz. The stimulus pulses were cathodic-first controlled-current pulse pairs, each phase 150 μs in duration. The amplitude of the stimulus pulse is listed near the right edge of each trace. In Figure 1A, the neuronal response (circled) had a well-defined threshold (approximately 8 μA) and the amplitude of the response did not increase further as the amplitude of the stimulus pulses increased (Figure 1B). From these characteristics, we can conclude that this type of response was generated by a single corticospinal neuron with a well-defined excitation threshold, and whose axon passed very close to the recording electrode in the pyramidal tract. Figure 2A shows three examples of the second type of pyramidal tract response, which is graded over at least part of the range of stimulus amplitude. In Figure 2B, the amplitude of the earliest (leftmost) response component is plotted against pulse amplitude. The neuronal mechanisms that underlies this type of response are not entirely clear. These graded responses may represent the recruitment of more than one corticospinal neuron, but the fact that the response components occurs at well-defined latencies after the stimulus pulse argues against this interpretation. They may represent the action potentials from a single cortical neuron which is directly excited by the stimulus but which does not have a well-defined electrical threshold. Thus, action potentials may be generated only in response to some of the stimulus pulses, and the probability of a response increases with increasing stimulus amplitude,

causing the averaged responses to be graded, as in Figure 2B. The responses, which occur at a longer latency after the stimulus pulse (e.g., at 2.5 ms in Figure 2A), probably are generated by corticospinal neurons that are excited transsynaptically, as described below in greater detail. As the stimulus amplitude is increased, more neurons that contribute excitatory synaptic inputs to the corticospinal neurons may be recruited, thereby increasing the probability that the neuron will discharge an action potential after any given stimulus pulse.

As noted above, cortical stimulation can excite cortical neurons either directly or transsynaptically. Figure 3 shows the compound action potential that was evoked from a macroelectrode on the surface of the postcruciate gyrus and recorded in the ipsilateral pyramidal tract. The early response persists after the cortex is ablated, while the second response disappears after this lesion, thereby demonstrating that the late response represents neurons that are excited by intracortical (synaptic) mechanisms (Patton and Ammassian, 1954). In the adult cat, and with the recording electrode in the medullary pyramidal tract, the division between the early and late responses occurs at approximately 1.9 ms.

Figures 4 and 5 show the effects of 7 hours of continuous intracortical microstimulation on the pyramidal tract responses. In all of the examples cited below, 5 of the 7 microelectrodes in the array were pulsed in the interleaved mode. The response shown in Figure 4 (from cat IC-174) was of the partially-graded variety, while the response shown in Figure 5 (from IC-175) was of the essentially "all-or-none" type. The latency of both responses was less than 1.9 ms and therefore they both were probably evoked directly the intracortical microstimulation, rather than transsynaptically. In both examples the threshold of the response was quite low before the 7-hours of continuous stimulation (6 μA in Figure 4A, 10 μA in Figure 4B). In cat IC174, 5 of the microelectrodes were pulsed in the interleaved mode at an amplitude of 11 μA (1.6 nC/ph) and at a rate of 50 Hz per electrode. This rather low level stimulation induced no discernible effect on the threshold of the pyramidal tract response. In Figure 5, pulsing 5 microelectrodes in the interleaved mode, at a higher amplitude (26.5 μA, 4 nC/ph) for 7 hours at 50 Hz, induced a modest increase in the threshold of the

pyramidal tract response. In general, the intracortical microstimulation caused a greater increase in the threshold of the longer-latency responses, which probably correspond to corticospinal neurons that are excited transsynaptically. Figure 6 shows the effect of 7 hours of stimulation at 26.5 μA (4 nC/ph) on a response with a latency of 2.6 ms. The 7-hour stimulation regimen caused the response threshold to increase to above 32 μA, from its initial value of 12 μA.

Figure 7 summarizes the data of the type depicted in Figures 4-6, for 19 pyramidal tract response components recorded from 4 cats (IC167, 173, 174, 175). The abscissa is the threshold of the response before the 7-hour stimulation regimen, and the ordinant is the threshold after the regimen. The thresholds were measured immediately before and within 30 minutes after the end of the stimulation. The solid line is the locus of X=Y (no change in the threshold of the response as a result of the 7 hours of stimulation). Figure 7A shows data from 12 response components whose latency was less than 2 ms and which, therefore, probably represent corticospinal neurons that were excited directly by the microstimulation. In all of these experiments, the 7 hours of microstimulation was continuous, and 5 (of the 7) microelectrodes in the array were pulsed in the interleaved mode with cathodic-first, controlled-current pulse pairs, in which each phase was 150 μsec in duration. The pulse repetition rate was either 50 or 25 Hz per electrode, and the stimulus amplitude was either 26.5 μA, 16 μA or 11 μA. There is no clear correspondence between the stimulus frequency and/or amplitude applied during the 7 hours of stimulation and the increase in the threshold. The clearest trend is between the effect of the stimulation on the response threshold and the response's prestimulus threshold. If the prestimulus threshold was 10 μA or greater, then 7 hours of stimulation produced relatively little elevation (in some cases, no elevation) in the response threshold, even when the stimulus amplitude and pulse rate were quite high (26.5 μA, 4 nC/ph, and 25-50 Hz). Neurons whose threshold initially was low (2-9 μA) and which probably were closer to the stimulating microelectrodes, sometimes exhibited a considerable increase in their electrical excitation threshold, even when the continuous stimulation was at a low amplitude.

Figure 7B shows the effects of the 7 hours of stimulation on the threshold of

pyramidal tract components whose post-stimulus latency was greater than 2 ms and which, therefore, probably represent corticospinal neurons that were excited transsynaptically. In general, the 7 hours of stimulation produced a markedly increase in the threshold of these responses, even when their prestimulus thresholds were high.

The stimulation-induced depression of neuronal excitability (SIDNE) may be related to the aggregation of lymphocytes around the pulsed microelectrodes. The aggregates may become very dense immediately adjacent to the microelectrodes, but they rarely extend more than about 200 μm from the pulsed tips. However, as noted below, the SIDNE persists for many days after the end of the stimulation, and this tends to argue against its being caused by the aggregation of the lymphocytes, which dissipate completely within 3 days after the end of the stimulation.

Figure 8 illustrates the long persistence of the SIDNE. Figure 8A shows the responses recorded from microelectrode #4 of cat IC175. It is virtually certain that this "all-or-none" response was generated by a single corticospinal axon passing close to the recording microelectrode. Its latency was approximately 1.8 ms after the stimulus pulse, so the neuron probably was excited directly by the intracortical microstimulation. The response first appeared at 84 days after implantation of the intracortical array and its threshold gradually decreased to 6 μA by day 160. At this time, the electrode was pulsed for 7 hours at 50 Hz, at a pulse amplitude of 26.5 μA and 4 nC/phase (Figure 8B). Immediately after the 7 hours of stimulation, the neurons' threshold was elevated to above 32 μA. The neuron's excitability recovered gradually, and by 28 days after the stimulation, its threshold had returned to 6 μA, the pre-stimulus value. Thus, the 7 hours of continuous stimulation was not lethal to this neuron, which much have been very close to the stimulating microelectrode, but the stimulation did induce a very persistent change in its electrical excitability.

<u>The stability of the excitation threshold of cortical neurons activated by chronically-implanted intracortical arrays.</u>

High-density intracortical microstimulation arrays have the potential to activate very small populations of cortical neurons, as would be required for a visual prosthesis

based on intracortical microstimulation. Ideally, the excitation threshold of neurons close to each microelectrode should remain stable for many weeks or months, so that the same small population of neurons is activated consistently by each microelectrode The data presented in this report indicates that our "floating" arrays have not yet achieved this ideal objective.

Figure 9A shows the response growth function of an "all-or-none" type of response evoked from microelectrode #4 in cat IC-174. Based on its long post-stimulus latency (3 ms), the corticospinal neuron probably was excited transsynaptically. At 91 days after implantation of the array, the response threshold was approximately 8 μA, but it had increased to 12 μA by day 105 and to approximately 28-32 μA by day 125. Figure 9B shows the growth function of a response evoked from microelectrode #4 in cat IC-175. The large response appeared 84 days after implantation of the array, and its threshold decreased gradually, to approximately 6 μA by day 146. At day 160, with the threshold still at 6 μA, the electrode was pulsed continuously for 7 hours, as part of one of the experiments described in the previous section. It is noteworthy that in both Figure 9A and 9B, the maximum amplitude of the responses was quite constant over the interval in which the response could be identified (34 days in Figure 9A, 62 days in Figure 9B). This testifies to the stability of the recording electrode in the pyramidal tract.

Figures 10A-10H are plots of the threshold of 10 responses evoked from microelectrodes in cats IC174 and 175, the two animals in which the intracortical arrays were implanted for the longest interval. The responses were identified and tracked over the interval of many days by their unique post-stimulus latencies. The threshold of most of the responses was not stable over many days. Thus, the response shown in Figure 10A was first detected on the 30th day after implantation of the array and it disappeared after day 50. The responses depicted in Figures 10B, C and D could be recorded only during 2 successive sessions, spanning 15 to 20 days. Some responses could be identified over a longer interval. The response depicted in Figure 10E appeared on the 30th day after implantation, and finally disappeared after day 126. The responses with higher thresholds tended to be more stable (Figure 10F). This is

perhaps understandable, since the neurons responsible for these high-threshold responses probably were never very close to the stimulating microelectrode, and thus would have been less sensitive to small movements of the electrodes.

On the basis of the limited data available at this time, it appears that the responses become somewhat more stable after the arrays have been in place for a long period of time. Thus, Figures 10G and 10H show 2 responses evoked from electrode #4 in cat IC-175. Both of these responses appeared at approximately day 84 and were present for 78 days, at which time the cat was used in a stimulation study. We were still monitoring the recovery of their thresholds, now 182 days after implantation of the array.

There is histologic evidence that the microelectrode arrays do move through the cerebral cortex after implantation. Figure 11 shows a tissue section through the postcruciate gyrus of cat IC-174, which was sacrificed 168 days after implantation of the array. The plane of the section is parallel to the surface of the cortex and perpendicular to the axis of the microelectrodes, and approximately 300 μm above the microelectrode's tip. The linear glial scar extending to the right of the microelectrode track (TR) suggests that the electrodes had been moving through the tissue. However, the scar is well healed, and it is uncertain whether the tissue injury occurred during implantation of the array or subsequent to implantation, and therefore, whether it would have been responsible for the instability of the neuronal response thresholds depicted in Figures 10A and 10B, recorded from this animal. By 80 days after implantation, the array matrices are encapsulated with connective tissue, and we would expect that this would stabilize the array against further movement. In our most recent implant (IC176), we have modified our implantation procedure with the objective of improving the array's stability. The array was implanted rapidly into the cortex at a velocity of approximately 1 meter/sec, so as to cause less dimpling and displacement of the cortex and, thus, less risk of slashing the cortical tissue. Also, we have replaced our "cap" of silastic artificial dura with a layer of fascia resected from the temporalis muscle. This fascia is softer and more flexible than the silastic artificial dura, and conforms better to the contour of the array matrix and its cable. We are hopeful that this will reduce the tendency for the

array to be slowly displaced by continuing downward pressure exerted by the silastic cap.

REFERENCES

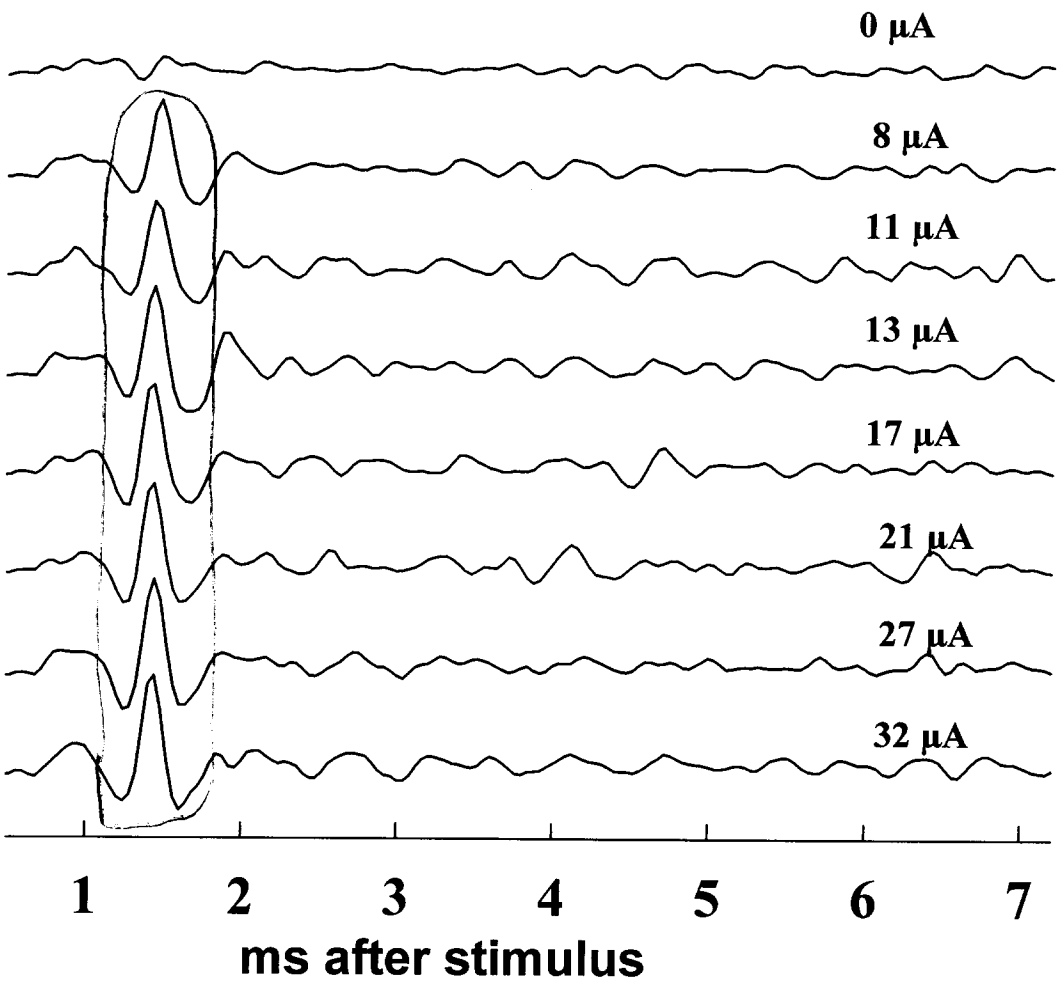
Patton, H.D and Amassian, V.E. "Single- and multi-unit analysis of the cortical stage of pyramidal tract activation" *J. Neurophysiology, 17:345-363 (1954)*

WORK FOR NEXT QUARTER

In the next report, we will present the histologic results of intracortical stimulation of the animals whose physiologic results are described above. We will also begin implantation of intracortical arrays of 19 discrete iridium microelectrodes .

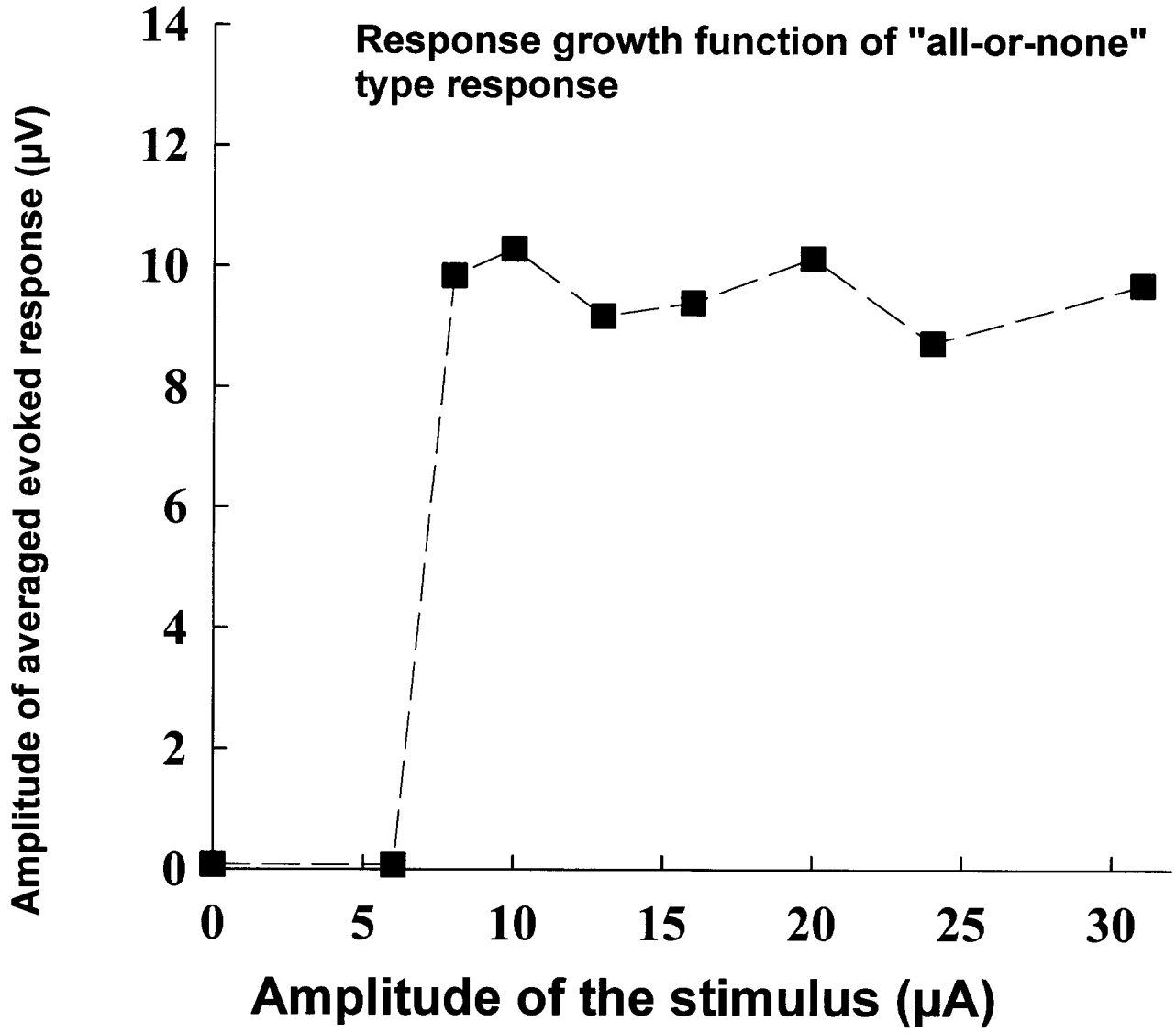
cat ic174 36 days after implantation

"All-or-none" type response
evoked in pyramidal tract, from intracortical microelectrode 3



ic/ic174b.spw

Figure 1A

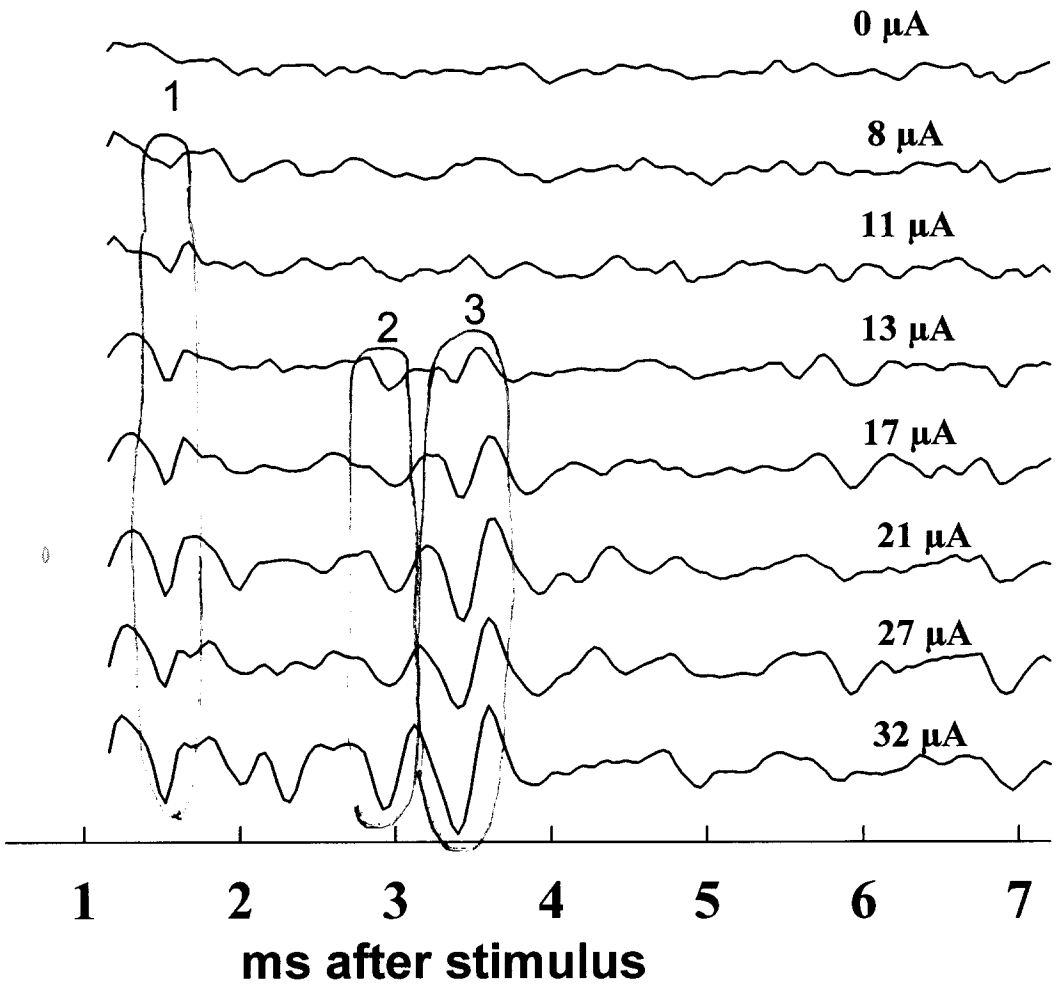


rapid.spw

Figure 1B

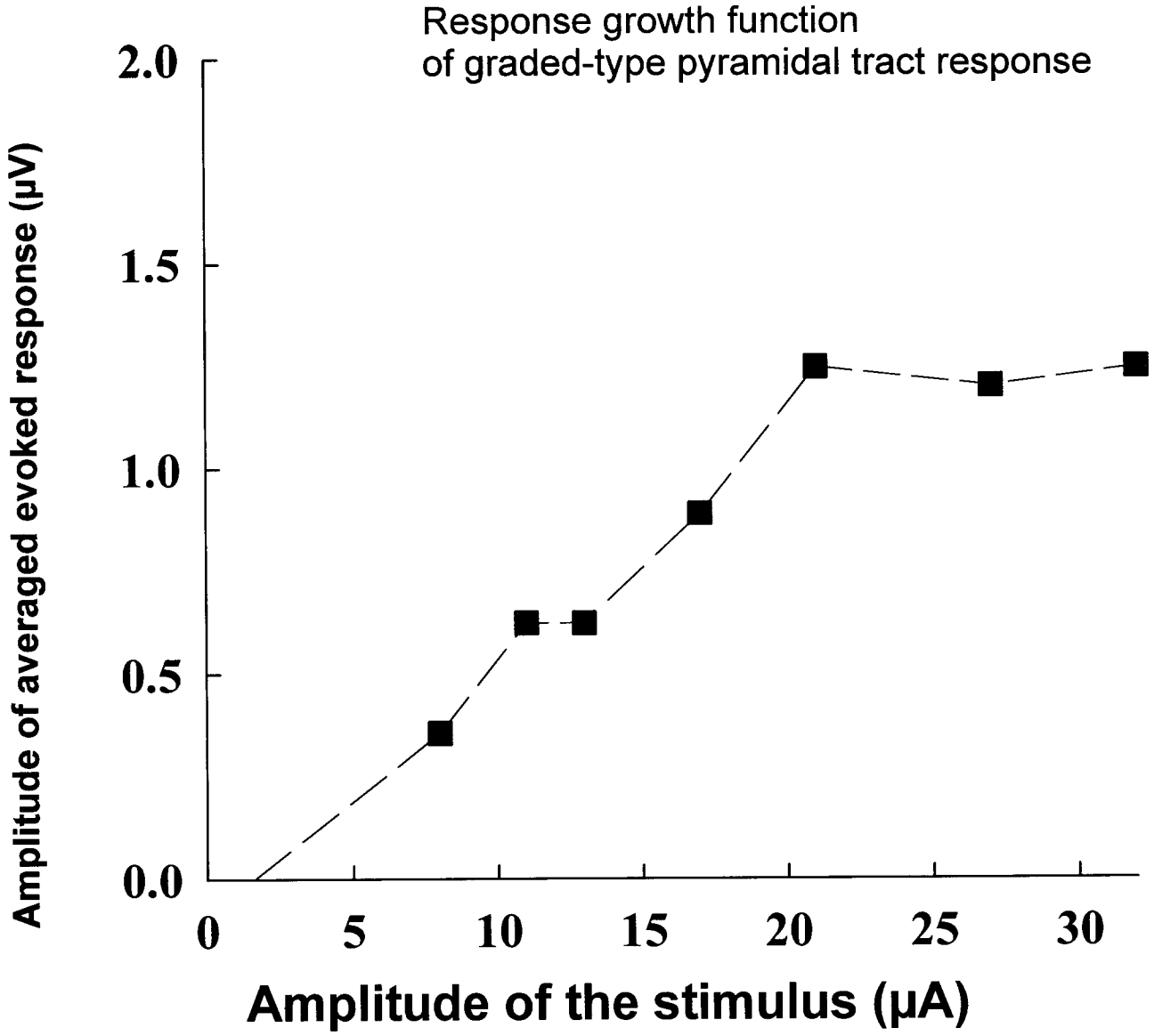
cat ic173 73 days after implantation

Pyramidal tract responses evoked from microelectrode 5



ic173a.spw

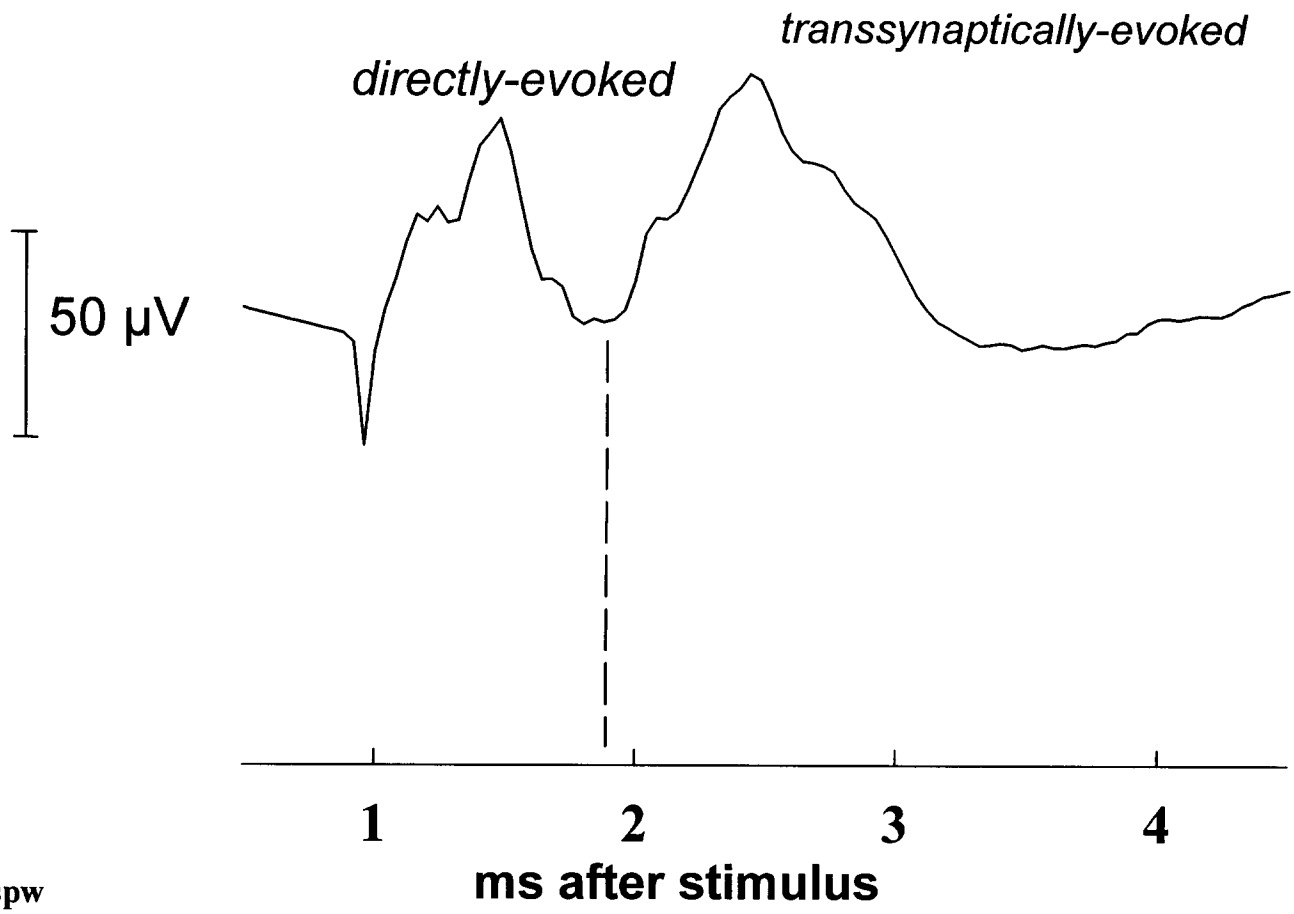
Figure 2A



gradual.spw

Figure 2B

compound pyramidal tract potential
evoked by macroelectrode on surface of sensorimotor cortex



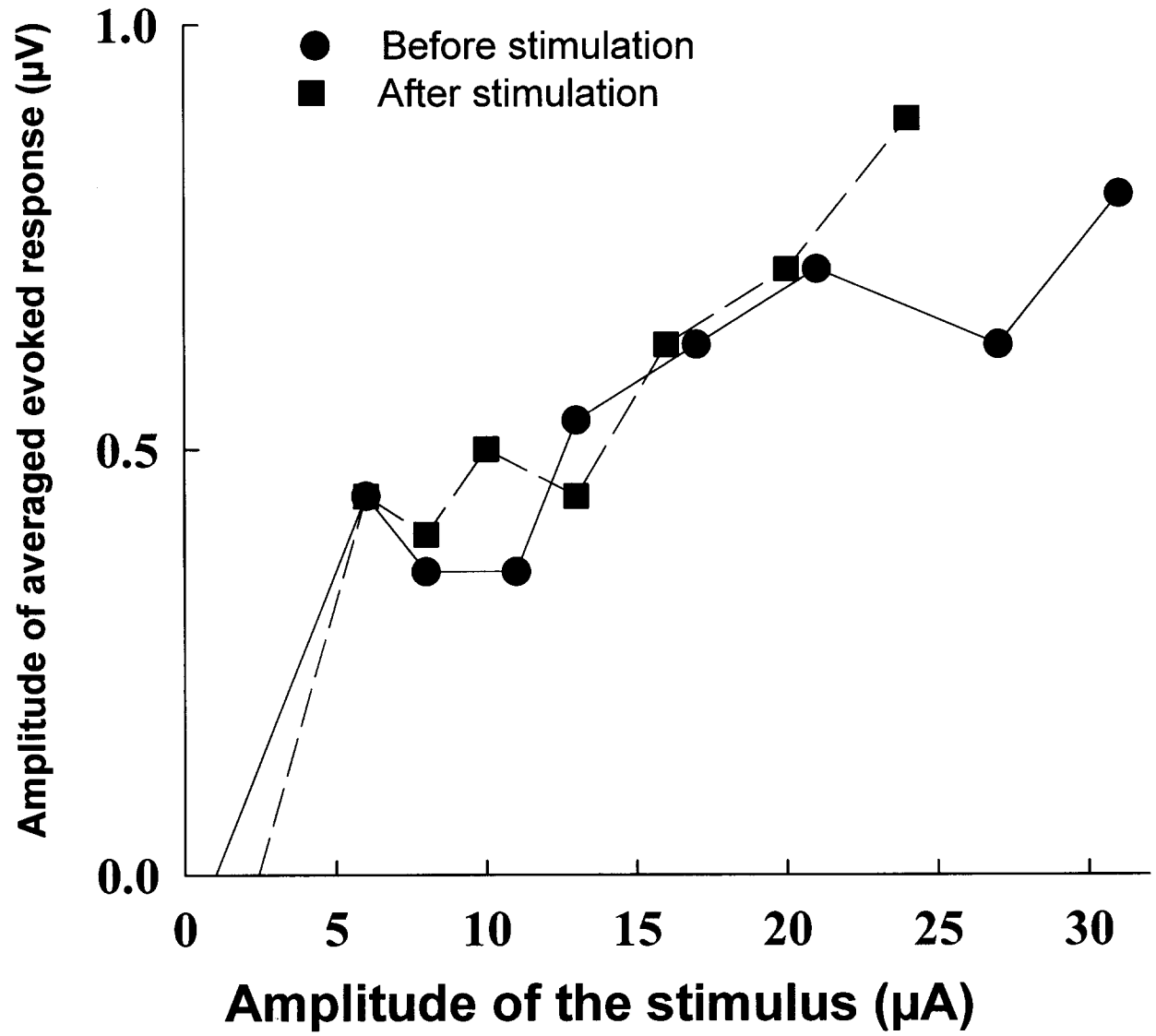
pyram.spw

Figure 3

cat ic174 Sept 30, 1998
Effect of 7 hours of stimulation on a
pyramidal tract component with latency of 1.88 ms

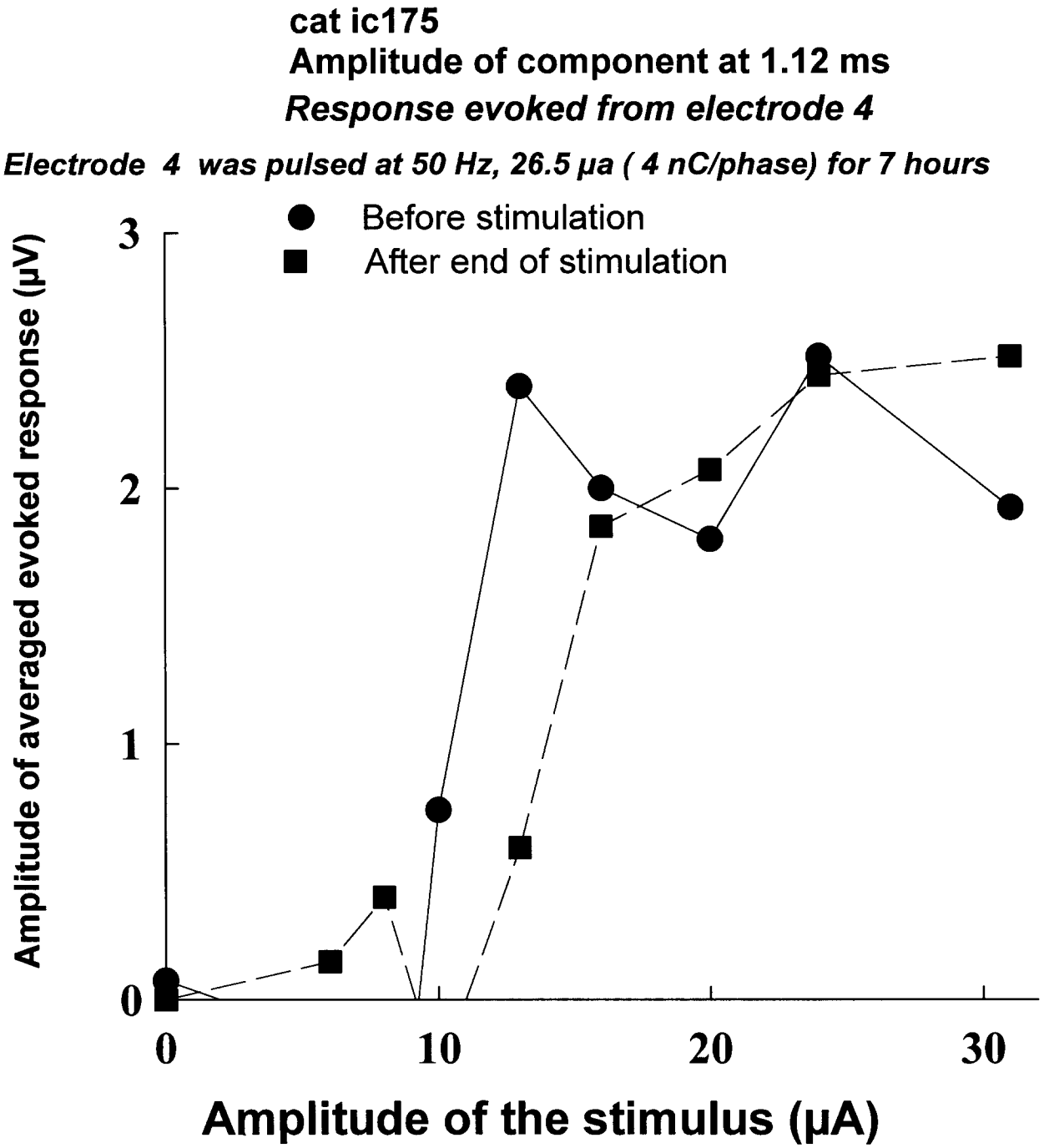
Response evoked from electrode 5

Electrodes 2,3,4,5 were pulsed at 50 Hz, 11 μa (1.6 nC/phase) for 7 hours



ic174s7.spw

Figure 4



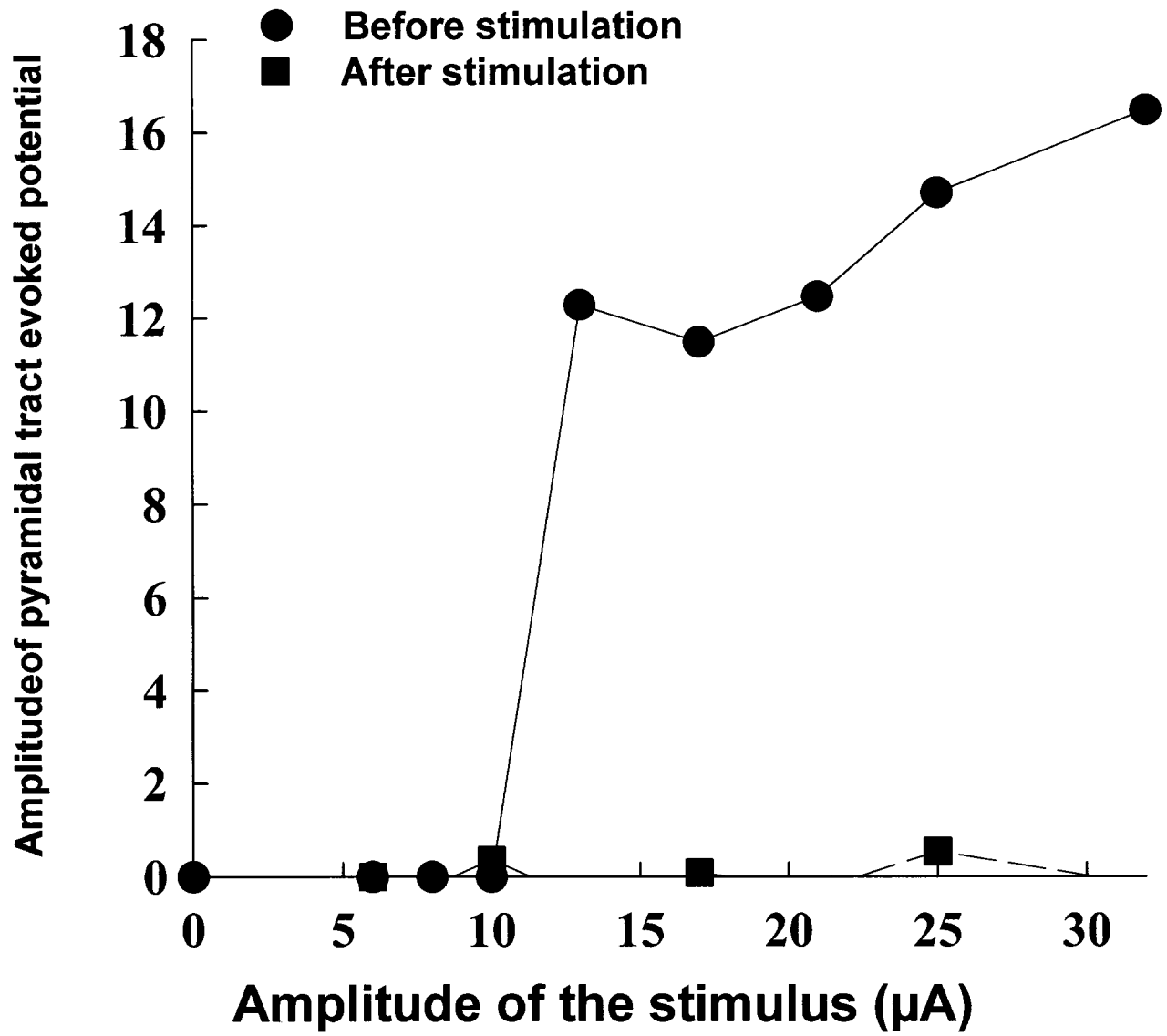
ic175s2b.spw

Figure 5

cat IC167 on Feb 2, 1998

Effect of 7 hours of stimulation on
the response with post-stimulus latency of 2.6 ms
evoked from microelectrode 5

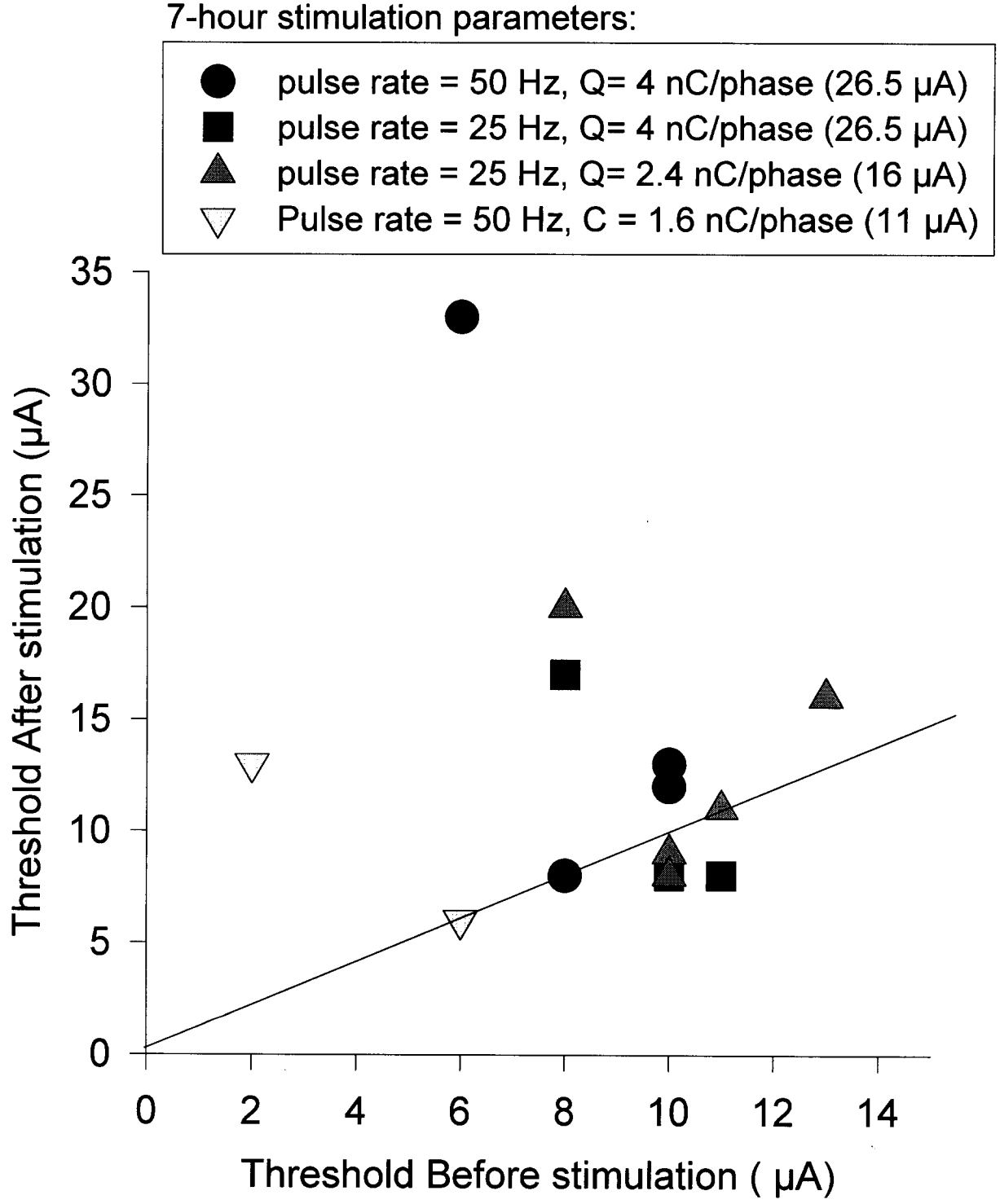
Electrodes 3,4,5,6,7 pulsed for 7 hours at 50 Hz,
and 26.5 µA (4 nC/phase) interleaved mode



ic167s2.spw

Figure 6

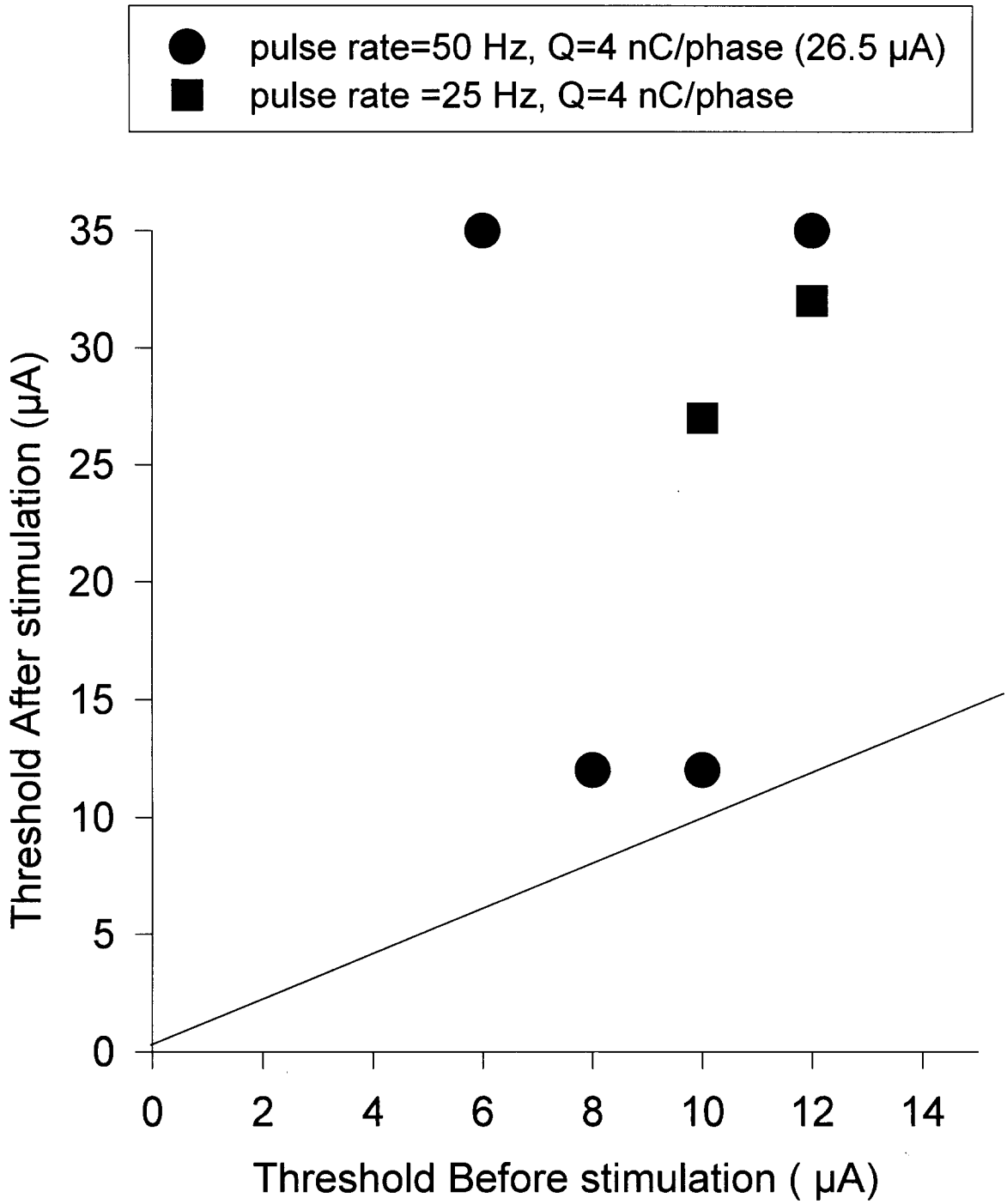
The effect of 7 hours of intracortical microstimulation on the threshold of pyramidal tract responses (Response latency < 2 ms)



c:\spw\wrkshp98\intracor\thresh1b.spw

Figure 7A

The effect of 7 hours of intracortical microstimulation on the threshold of pyramidal tract responses (Responses with post-stimulus latency > 2 ms)

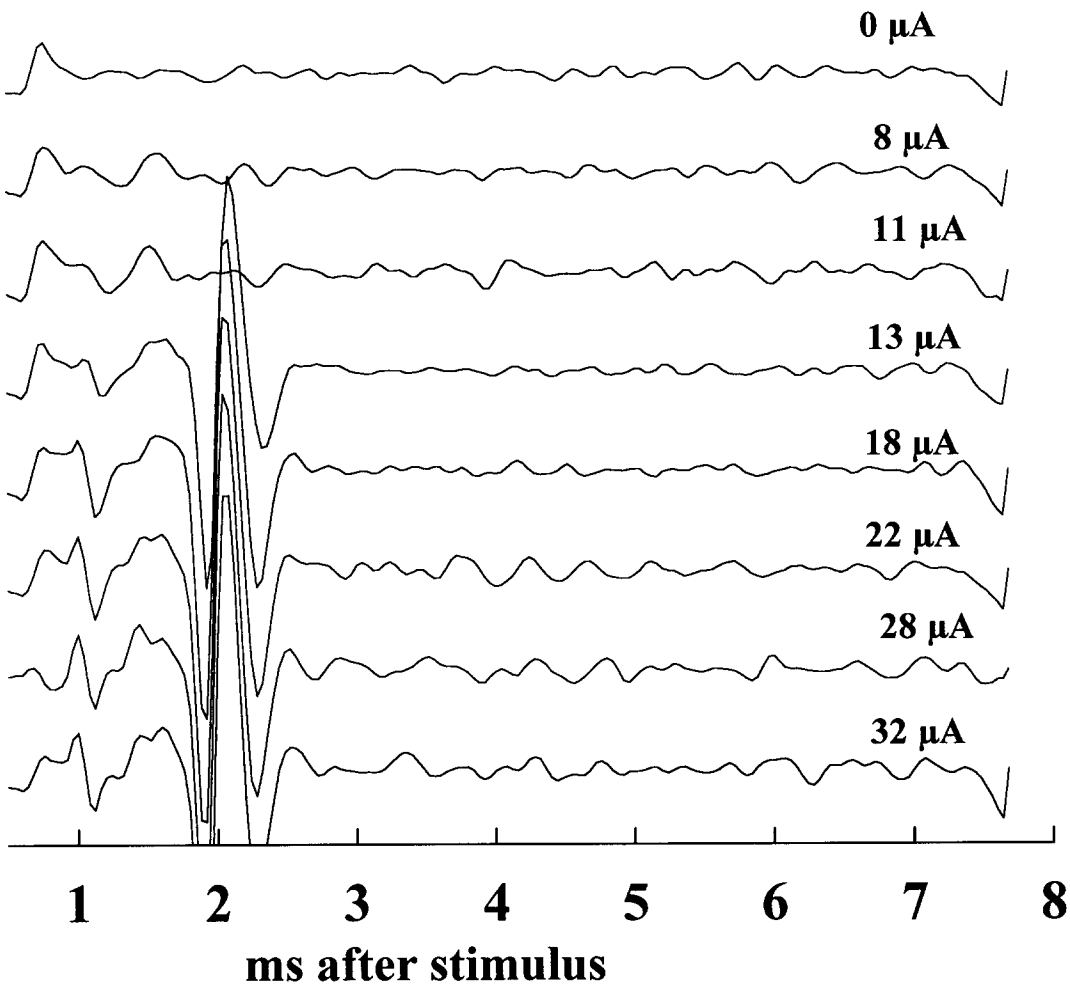


:\spw\wrkshp98\intracortical\icthres2.spw

Figure 7B

ic175, 118 days after implantation

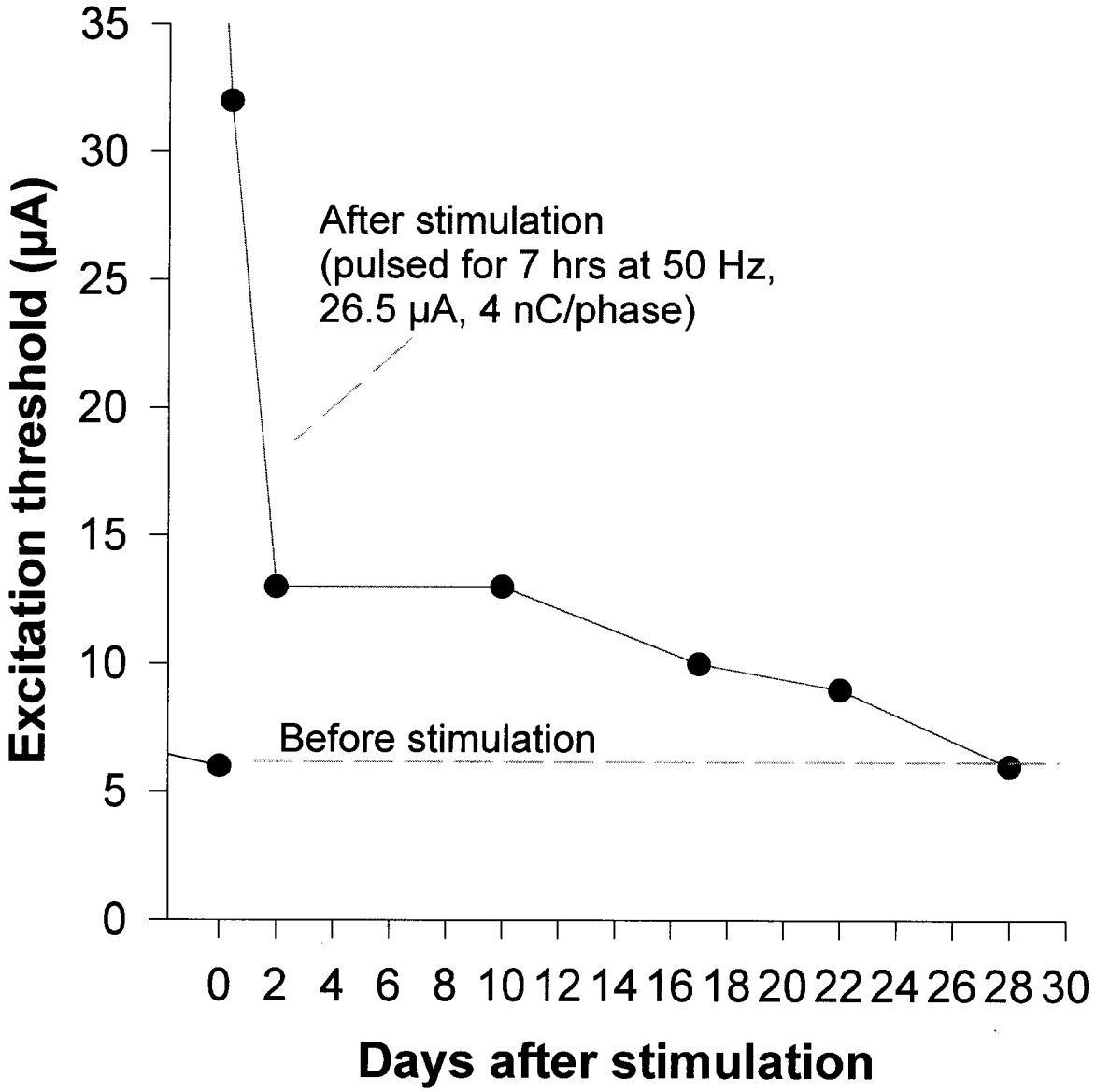
Pyramidal tract response evoked from electrode 4



ic/ic175h4.spg

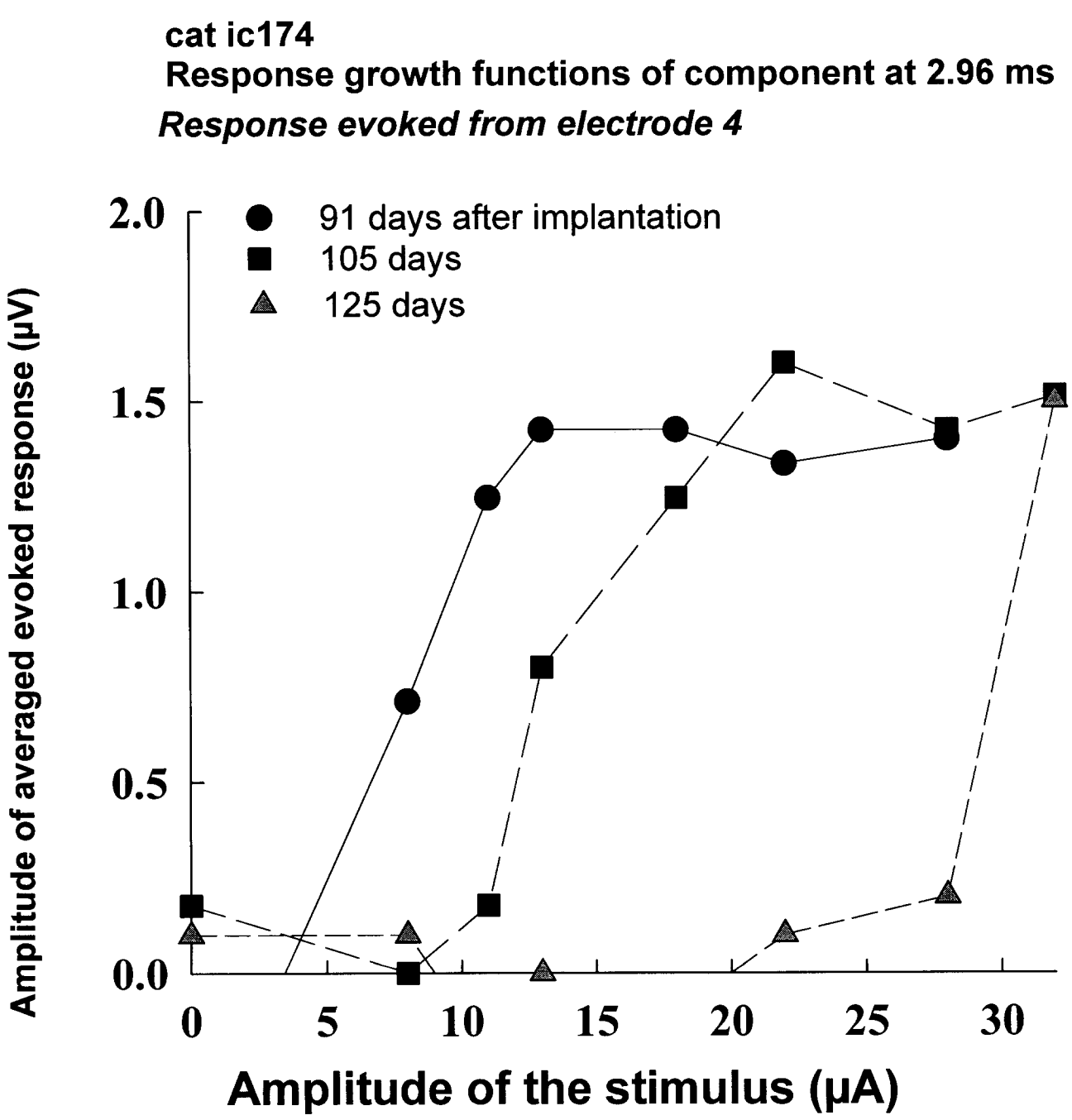
Figure 8A

cat ic175
Effect of 7 hours of stimulation on the component at 1.88 ms evoked in pyramidal tract from electrode #4



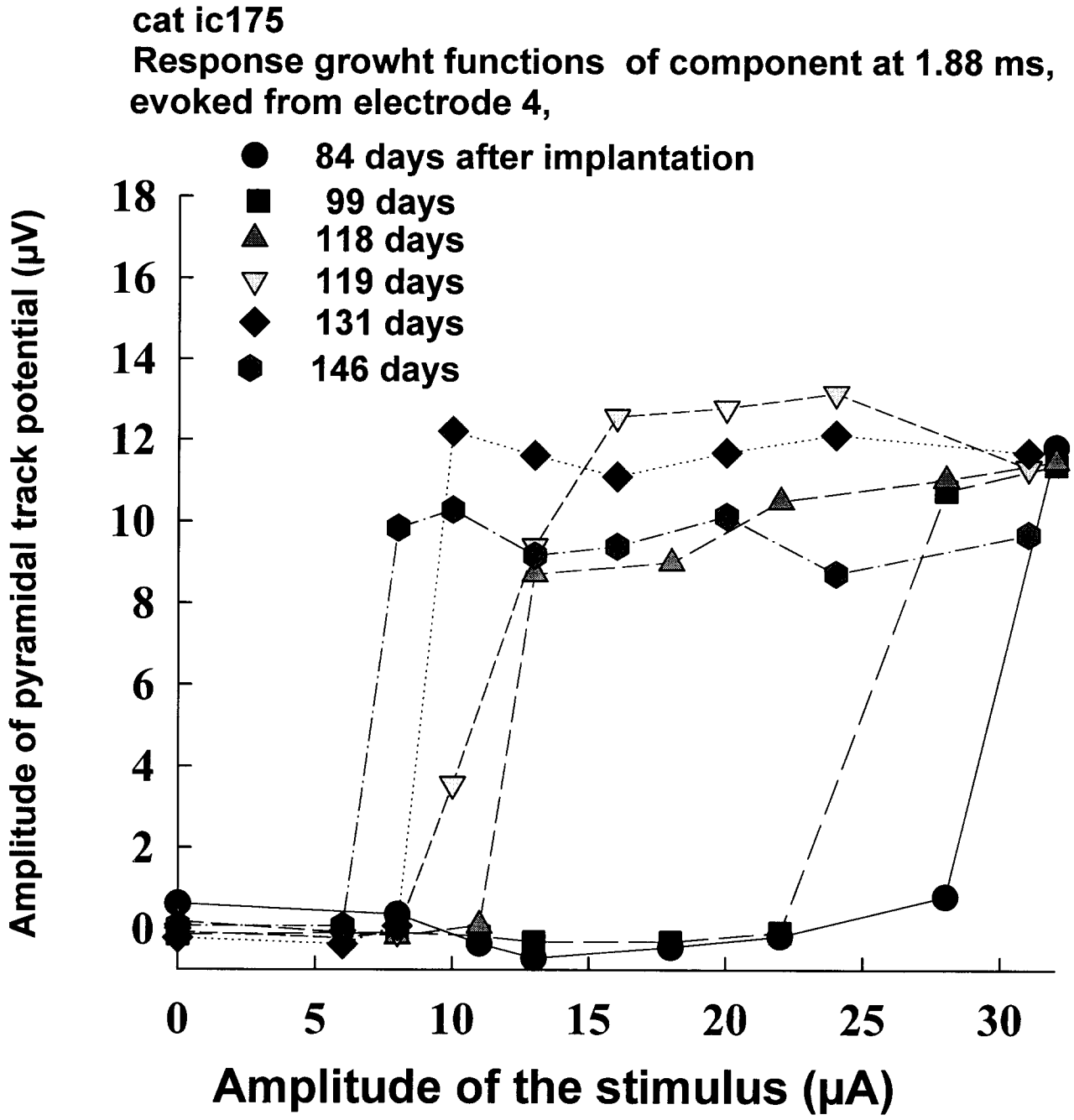
175sidne.spw

Figure 8B



ic174st4.spw

Figure 9A



ic175h4b.spw

Figure 9B

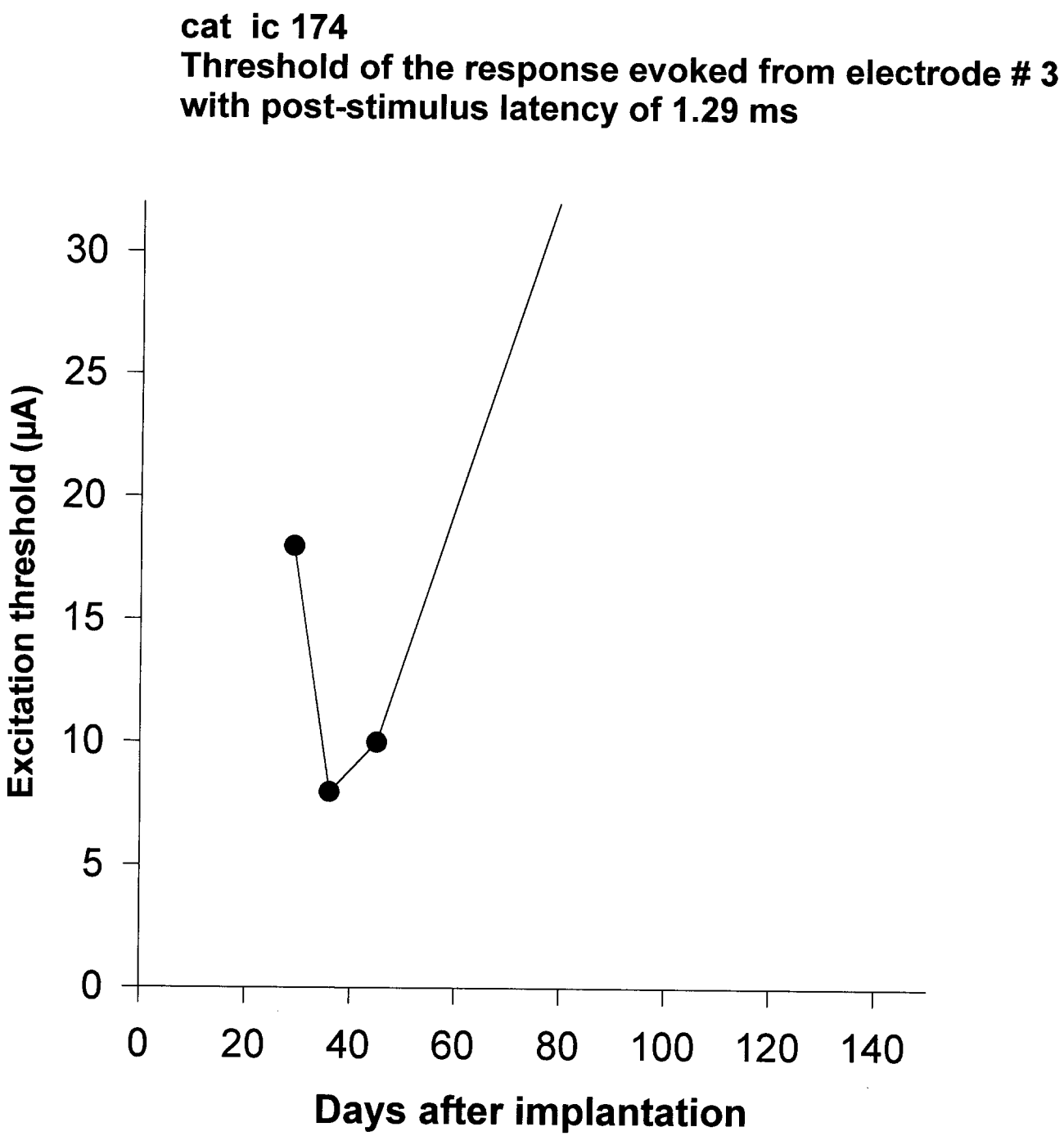

cat ic 174
Threshold of the response evoked from electrode # 3
with post-stimulus latency of 1.29 ms
Excitation threshold (µA)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
140
Days after implantation
173th3c.spw

Figure 10A

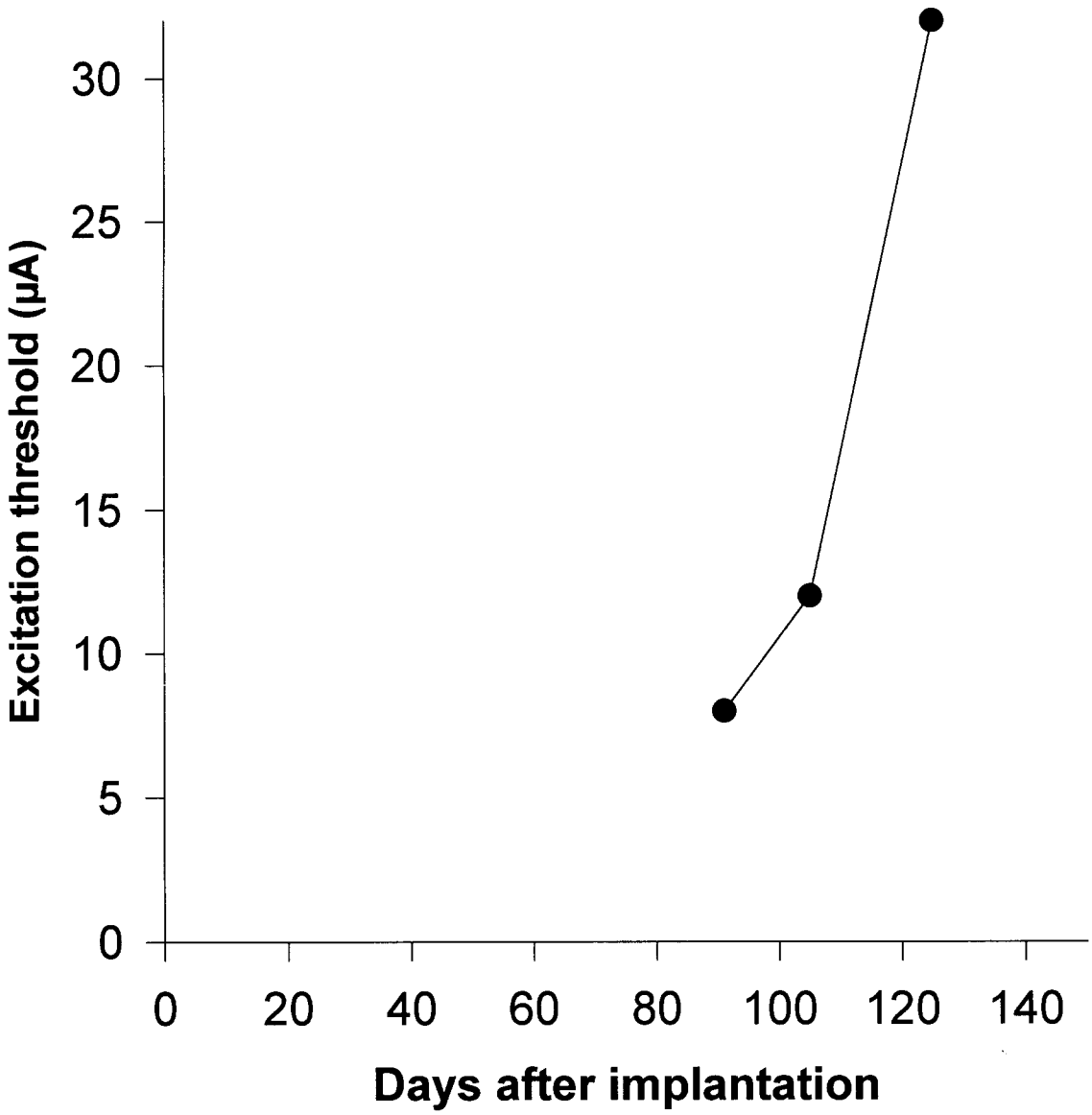

cat ic 174
Threshold of the response evoked from electrode # 4
with post-stimulus latency of 2.96 ms
Excitation threshold (µA)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
140
Days after implantation
174th4.spw

Figure 10B

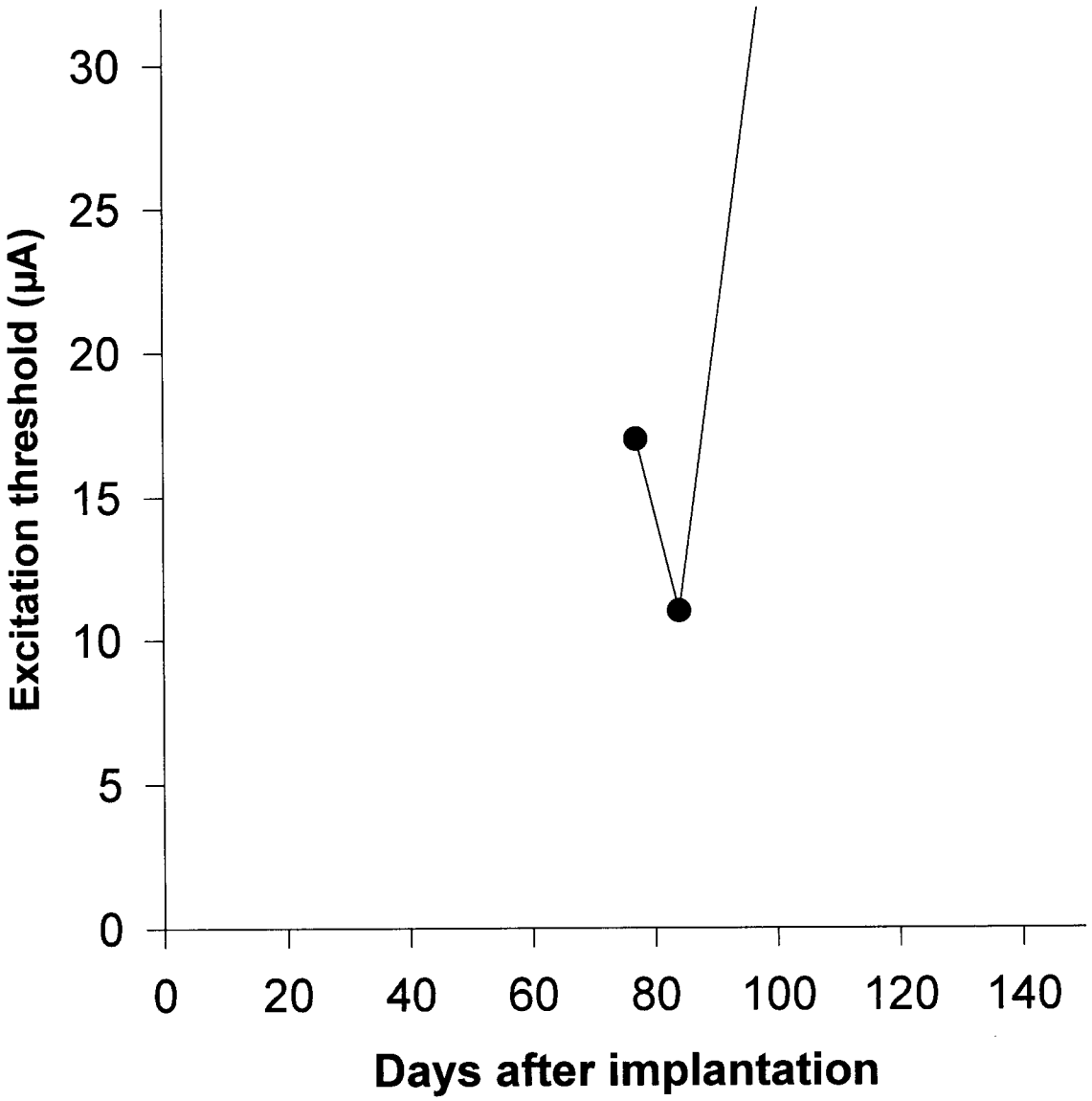

cat ic 175
Threshold of response evoked from electrode # 5
Component with post-stimulus latency of 1.92 ms
Excitation threshold (µA)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
140
Days after implantation
175th5g.spw

Figure 10C

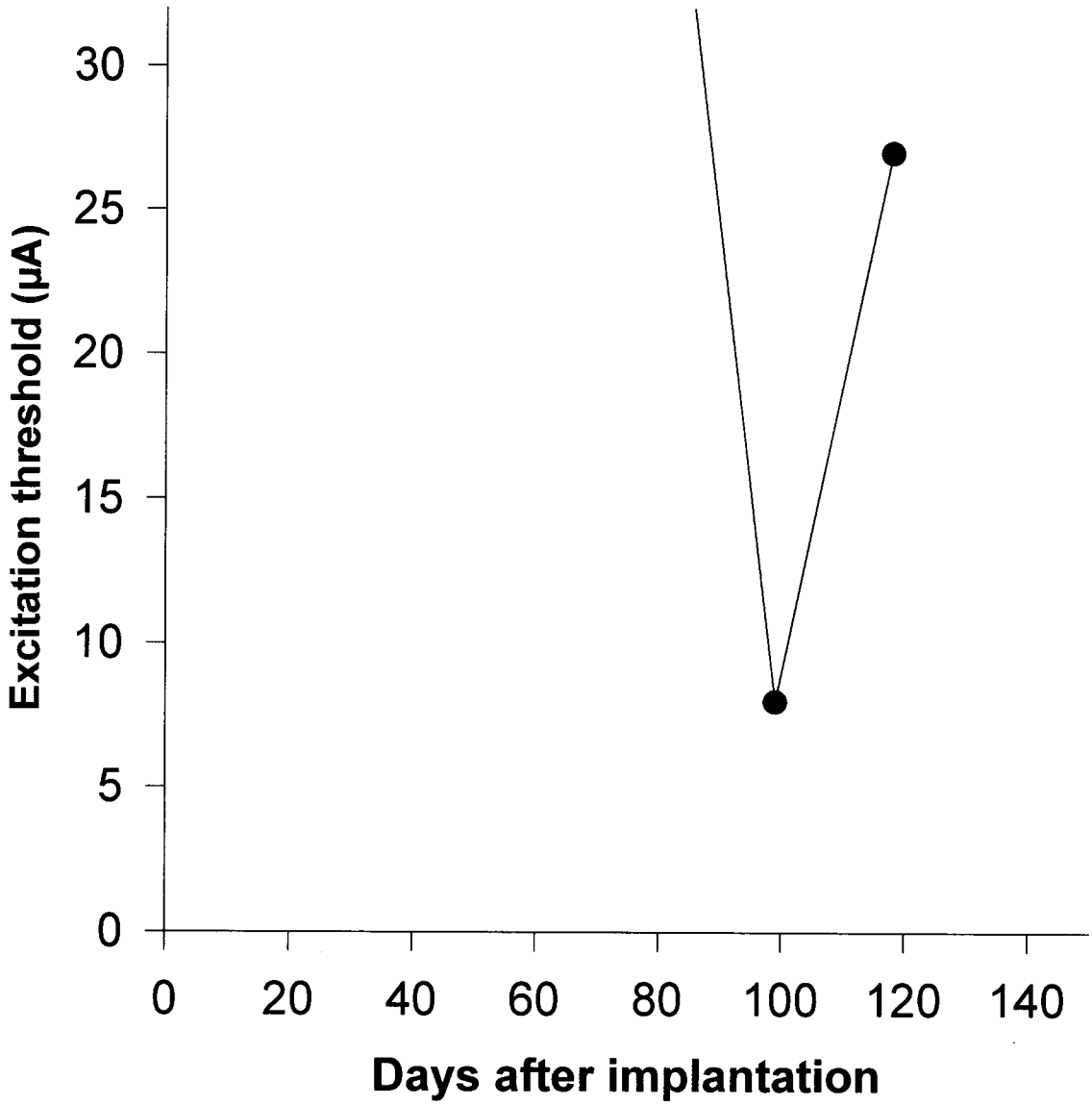

cat ic 175
Threshold of response evoked from electrode # 7
Component with post-stimulus latency of 2.92 ms
Excitation threshold (µA)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
140
Days after implantation
175th7b.spw

Figure 10D

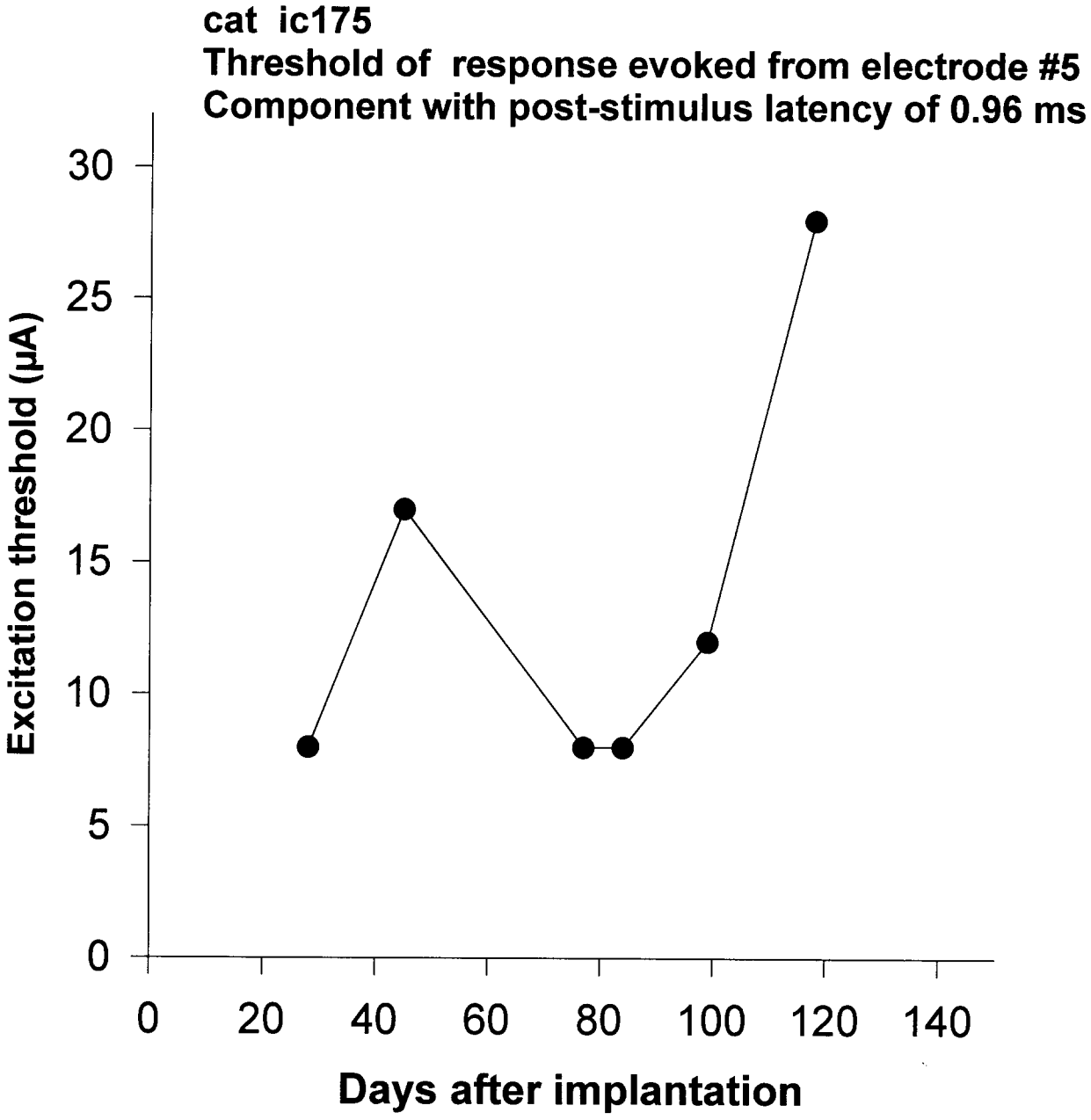

cat ic175
Threshold of response evoked from electrode #5
Component with post-stimulus latency of 0.96 ms
Excitation threshold (µA)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
140
Days after implantation
175th5e.spw

Figure 10E

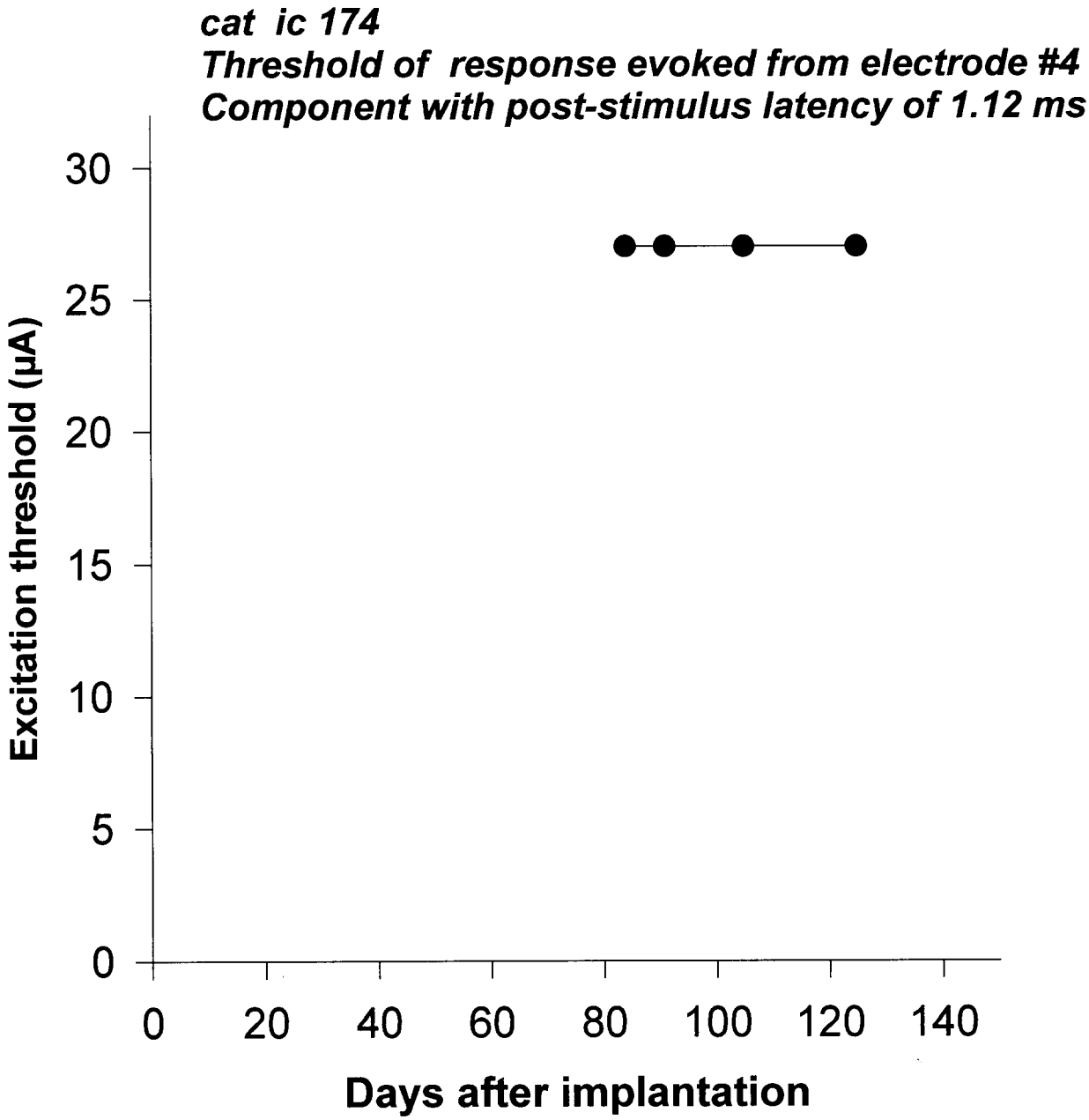

cat ic 174
Threshold of response evoked from electrode #4
Component with post-stimulus latency of 1.12 ms
Excitation threshold (µA)
30
25
20
15
10
5
0
0
20
40
60
80
100
120
140
Days after implantation
174th4g.spw

Figure 10F

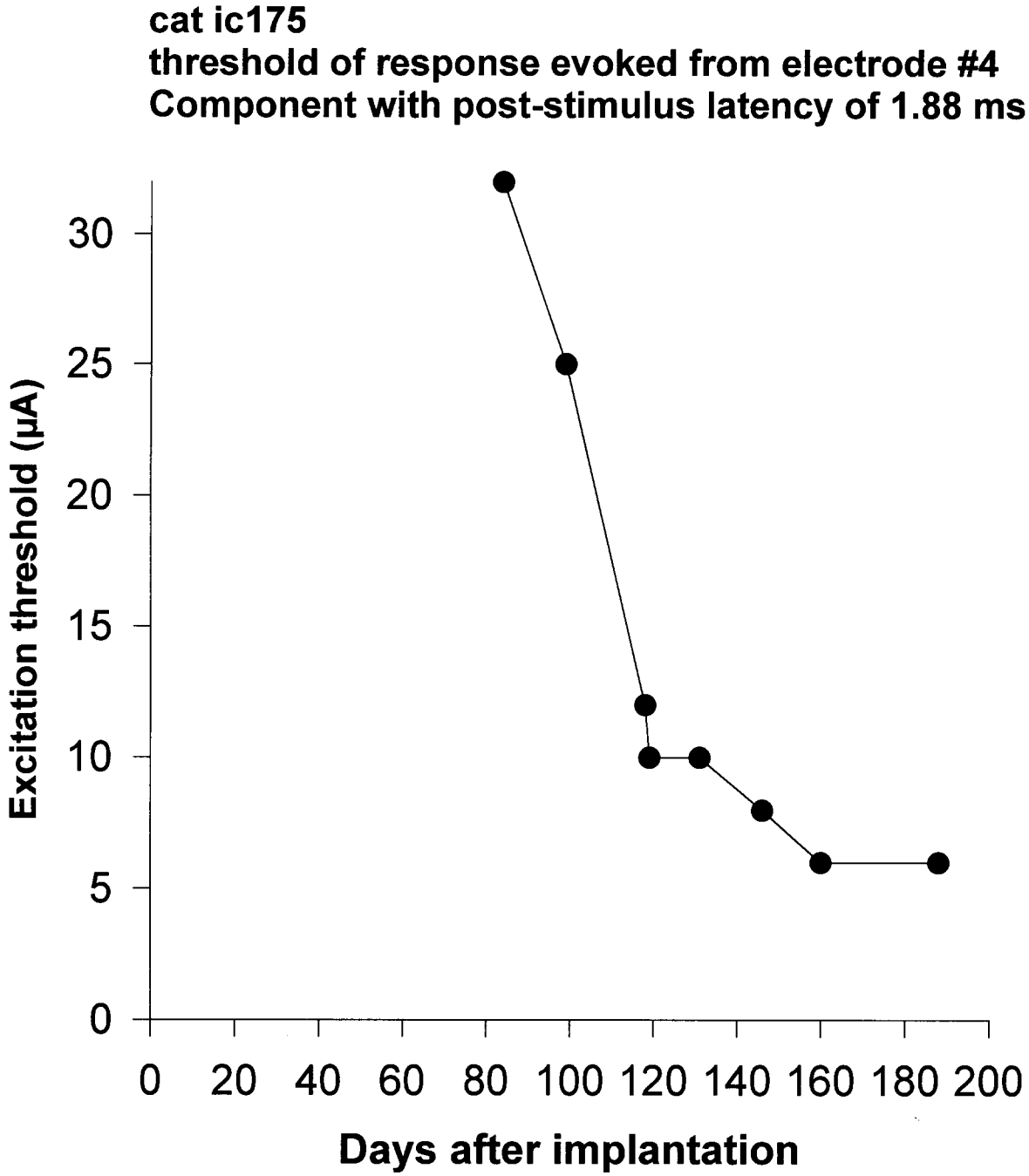
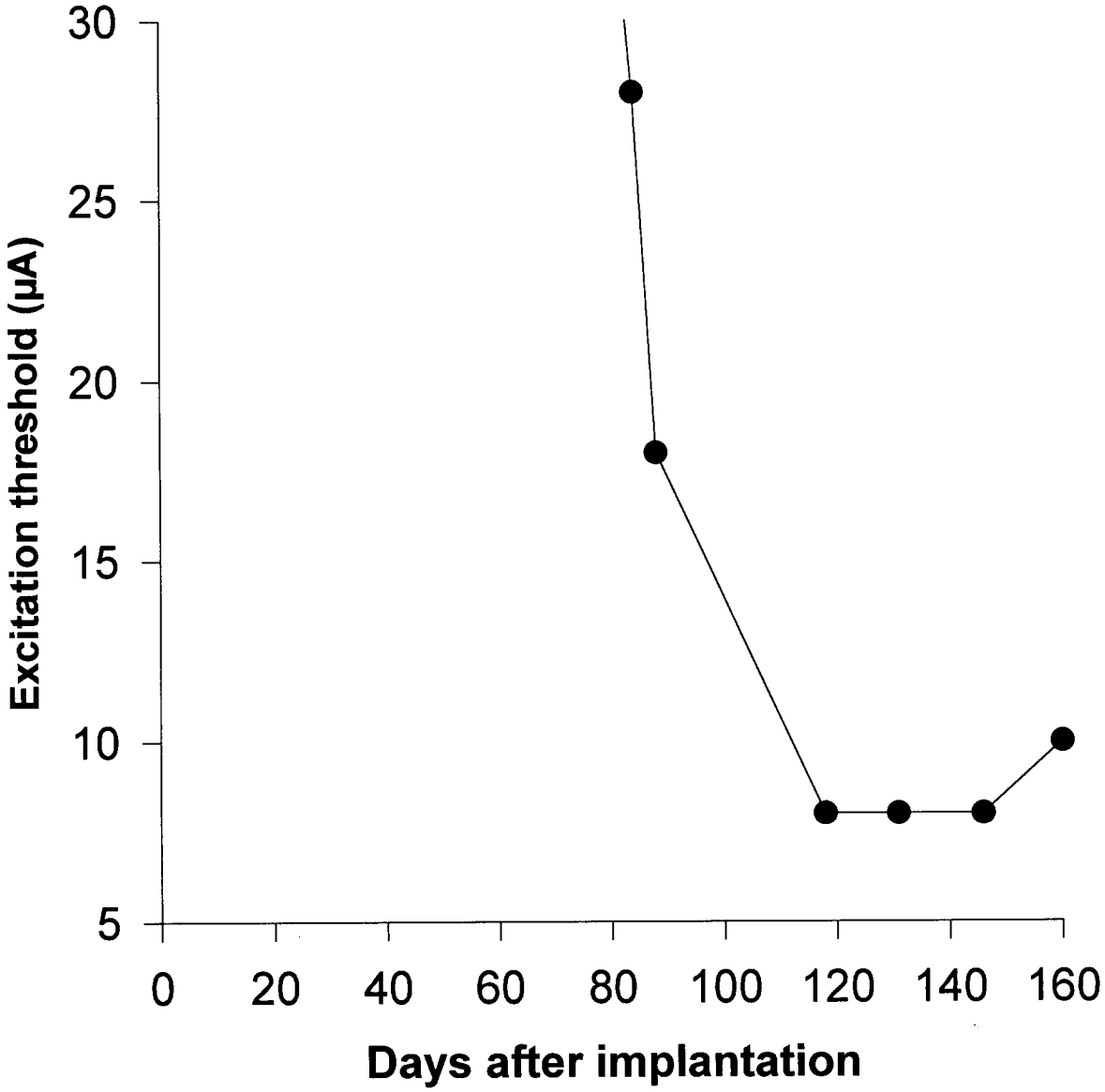

cat ic175
threshold of response evoked from electrode #4
Component with post-stimulus latency of 1.88 ms
Excitation threshold (µA)
0
5
10
15
20
25
30
0 20 40 60 80 100 120 140 160 180 200
Days after implantation
175th4a.spw

Figure 10G

cat ic175
threshold of response evoked from electrode #4
Component with post-stimulus latency of 1.12 ms



175th4c.spw

Figure 10H